STUDIES ON THE APPLICATION OF NEW CHALCONE DERIVATIVES AND THEIR NANOCOMPOSITES

SYNOPSIS

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BY

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STUDIES ON THE APPLICATION OF NEW CHALCONE DERIVATIVES AND THEIR NANOCOMPOSITES

(Synopsis of the Ph.D. Thesis of Ms. HARSHITHA K.R. to be submitted for the award of Ph.D. degree under the Guidance of Prof. B.K Sarojini, Department of Industrial Chemistry, Mangalore University, Mangalagangothri-574199)

1. INTRODUCTION

Chalcones are very important biological compounds which are widely distributed in fruits, vegetables, tea, spices, soy based foods and other plant products. Chalcones constitute an important group of natural compounds that are especially abundant in fruits (e.g., citruses, apples), vegetables (e.g., tomatoes, shallots, bean sprouts, potatoes) and various plants and spices (e.g., licorice), many of which have been used for centuries in traditional herbal medicine [1]. Chalcones are one of the subclasses of flavonoid family. They are commonly known as yellow pigments in flowers, and are also widely distributed in various parts (roots, rhizomes, heartwood, buds, leaves, flowers, and seeds) from species of genera *Angelica, Sophora, Glycyrrhiza, Humulus, Scutellaria, Parartocarpus, Ficus, Dorstenia, Morus, Artocarpus* and so forth. Chalcone is an aromatic ketone and an enone that forms the central core for a variety of important biological compounds, which are known collectively as chalcones or chalconoids. They are also used as synthetic intermediates for the preparation of pharmaceutically active agents [2]. Chalcones are an important class of compounds which are good intermediates for the synthesis of various heterocyclic compounds like flavones, flavanones, flavanols, aurones, isoxazolines, anthocynins, pyrazolines, pyrimidines, quinoxalines, benzalcoumaranones. The biological and industrial applications of chalcones are also found to be significant. Due to the presence of chromophore –CO-CH=CH- and other auxochromes, chalcones are colored compounds which exhibit high reactivity due to α, β -unsaturated un saturation present in the compounds [3,4]. The present study entitled 'Studies on the Application of New Chalcone Derivatives and their Nanocomposites' has been deliberated in five chapters. The **Part-A** included the synthesis, characterization, *in vitro* and *in silico*

anticancer studies of chalcones and their heterocyclic derivatives whereas optical studies on chalcone dibromides, bischalcones and nanocomposites is described in **Part-B**.

Objectives of the proposed work:

- To synthesize and study the spectral and single crystal XRD with *in silico* and *in vitro* anticancer activities of ethoxy acetophenone derived chalcones.
- To utilize chalcones and chalcone dibromides in the synthesis of heterocycles and to study their *in silico* anticancer activity.
- To determine nonlinear optical properties of newly synthesized chalcone dibromides.
- To carry out optical studies on bischalcone derivatives and their nanocomposites.

A short explanation of the contents distributed in each chapter is described below

CHAPTER I: AN OVERVIEW ON DIVERSE METHODS OF SYNTHESIS AND APPLICATIONS OF CHALCONE DERIVATIVES

This chapter provides an overview on diverse methods of synthesis and applications of chalcone derivatives. Various synthetic routes and new strategies employed for chalcone synthesis is discussed. A brief overview of physical chemical and biological importance of natural and synthetic chalcone analogues are also included. Optical properties and fluorescent activity of chalcones are also discussed here.

A number of techniques and schemes were reported for the synthesis of these compounds. Aldol condensation and Claisen-Schmidt condensation hold high position [5]. Other renowned techniques included Suzuki reaction, Witting reaction, Friedel-Crafts acylation with cinnamoyl chloride, microwave irradiation and *mechanochemical synthesis* to name a few. These innovative techniques employ various catalysts and reagents including $SOCl_2$ natural phosphate, lithium nitrate [6], amino grafted zeolites, zinc oxide, water, Na_2CO_3, PEG400, silica sulfuric acid, $ZrCl_4$ and ionic liquid etc. The development of improved strategies for the synthesis of α, β- unsaturated carbonyl compounds is still in

demand. The best method for the synthesis of chalcones is the conventional Claisen-Schmidt condensation in the presence of aqueous alkaline bases [7-9].

Chalcones are being absorbed in the daily diet and appear to be promising cancer chemopreventive agents [10]. A wide range of biological activities have been attributed to chalcones, including antitumor, antimutagenic, anti-inflammatory, antioxidant, antifungal, antibacterial, antiprotozoal, analgesic, and gastric protective properties [11]. As for antitumor activity, chalcones exhibit various effects including anti-initiation, apoptosis induction, antiproliferation, antimetastasis, antiangiogenesis, and so forth. The substitution on either side of the ring A or B substantially influence the biological activity of the chalcone derivatives.

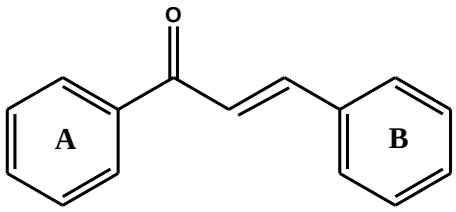


Figure 1: 1,3-Diphenyl-prop-2-en-1-one (Chalcone)

Chalcones and bischalcones are the versatile materials which were explored for different optical applications including second harmonic generation and third harmonic materials and in fluorescent probe for sensing various molecules. The organic molecule, like a chalcone underwent a strong delocalization of π-electrons in the conjugated system which signified its very high molecular polarizability and third order nonlinearities [12]. Hence chalcones were found to be immensely significant NLO materials since they possess prominent second and third-order nonlinearity properties [13-17]. The presence of carbonyl group acts as good electron acceptor in chalcones with the presence of donor/acceptor substituent in A and B rings which made chalcones as exceptional versatile materials in nonlinear optical and biological applications [18-20]. Materials owning third-order non-linear optical (NLO) coefficients have diverse applications in three dimensional (3D) optical data storage [21], lithographic micro fabrication [22],

fluorescence imaging [23], optical switching [24] and optical power limiting devices [25-27].

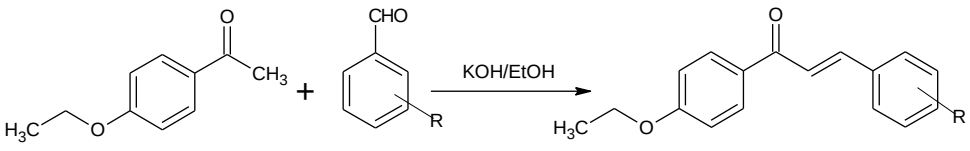
Highly specific interactions could be formed by halogen bond compared with classical hydrogen bonds. The introduction of bromo groups made chalcone thermally stable and come into picture as efficient materials to be used in optical instruments [28]. Bromo groups are introduced into chalcones to obtain chalcone dibromides. Bromo groups improve the molecular hyperpolarizabilities and could effectively reduce dipole-dipole interactions between the molecules [29,30]. The presence of bromo group improved the transparency and the thermal stability of the compounds. Chalcone dibromides usually have higher melting points and are thermally stable.

Eventhough number of heterocycles synthesized starting from chalcone dibromide the synthesis of triazolothiadiazine was lesser known. Owing to the biological importance of these derivatives the synthesis of them was undertaken. Usually, triazolothiadiazines were prepared by reaction of amino-mercapto-1,2,4-triazoles with α-bromochalcones. However, the direct condensation of chalcone dibromides reduced time and workup procedures.

Nanocomposite structures are used to generate optically functional materials. By the incorporation of semiconductor nanoparticles into polymer, glass, or ceramic matrix materials the optical properties including absorption, fluorescence, luminescence, and nonlinearity could be improved. The very small particle size was accountable for their improved optical properties. Nanomaterials have emerged as an area of interest motivated by potential applications of these materials in light emitting diodes, solar cells, polarizers, optical sensors, optical data communication and optical data storage.

Hence, it was decided to synthesize chalcone analogues starting from 4-ethoxyacetophenone with differently substituted benzaldehydes to understand the effect of various substitutions on B ring for the biological and optical activities. In addition, a study on the effect of delocalization by extended conjugation in bischalcones and chalcone dibromides were also carried out.

CHAPTER II: SYNTHESIS, SPECTRAL AND SINGLE CRYSTAL XRD CHARACTERIZATION WITH *IN SILICO* AND *IN VITRO* ANTICANCER ACTIVITIES OF ETHOXY ACETOPHENONE DERIVED CHALCONES



1-10

R=H, 4-F, 2-Cl, 3-Cl, 4-Cl, 4-Br, 3-NO_2, 4-NO_2, 4-OCH_3, 3,4-OCH_3.

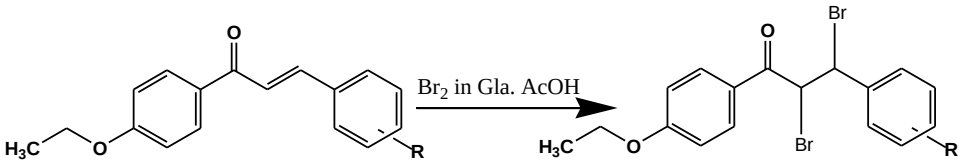
Scheme 1: Synthesis of chalcones

This chapter **[Scheme 1]** describes the synthesis**,** spectral characterization, *in vitro* biological evaluation and *in silico* studies of chalcone analogues. A series of chalcone scaffolds were synthesized by Claisen-Schmidt condensation of 4-ethoxyacetophenone with substituted aldehydes in basic medium. The formation of the synthesized compounds was confirmed by FTIR, ^{1}H NMR, ^{13}C NMR and Mass spectral data analysis. The *in vitro* anticancer activity of chalcone derivatives were evaluated against human breast cancer cell line (MDA-MB-231) and human melanoma cell line (A375) by MTT assay using Cisplatin as a reference drug. In order to know the binding efficiency, the chalcones were taken for docking studies on the active site of target inhibitor bound cytochrome P450 family oxidoreductase [PDB: 3PM0] for breast cancer and pirin inhibiting target [PDB: 3ACL] for skin cancer cell lines respectively. The pharmacokinetic profiling of chalcone scaffold against two targets was determined. Further detailed interactions and binding modes were investigated through MD simulations.

The single crystal XRD, Hirshfeld surface and frontier molecular orbital analysis of some 4-ethoxyacetophenone substituted chalcones were also discussed. The single crystals of 4-ethoxyacetophenone substituted chalcones were grown by slow evaporation technique from suitable solvent at room temperature. The intercontacts present in the crystal structure were visualized by Hirshfeld surface analysis. To determine the most reactive

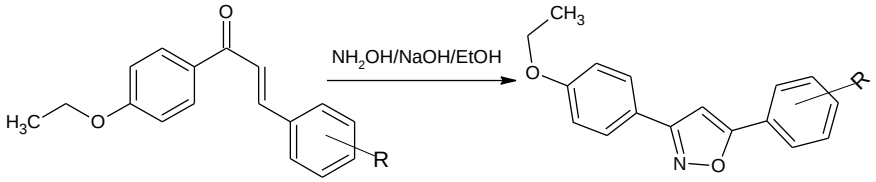
position in conjugated systems, electrical and optical properties frontier orbital gap was calculated.

CHAPTER III: UTILITY OF CHALCONES AND CHALCONE DIBROMIDES IN THE SYNTHESIS OF HETEROCYCLES AND THEIR MOLECULAR DOCKING STUDIES

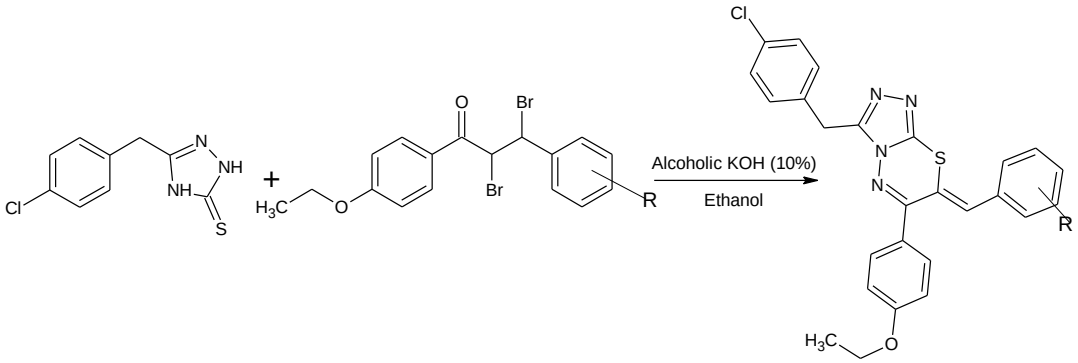


R=H, 4-F, 2-Cl, 3-Cl, 4-Cl, 4-Br, 3-NO_2, 4-NO_2, 4-OCH_3, 3,4-OCH_3.

Scheme 2: Synthesis of chalcone dibromides



Scheme 3: Synthesis of target isoxazoles
22 (R=4F); **23** (R=2Cl); **24** (R=3-Cl); **25** (R=4-Cl); **26** (R=4-Br)



Scheme 4: Synthesis of target triazolothiadiazines
32 (R=4F); **33** (R=2Cl); **36** (R=4-Br); **39** (R=4-OCH_3)

The reaction of chalcone with bromine in acetic acid medium resulted in the formation of chalcone dibromides **[Scheme 2]**. The formation of the newly synthesized compounds

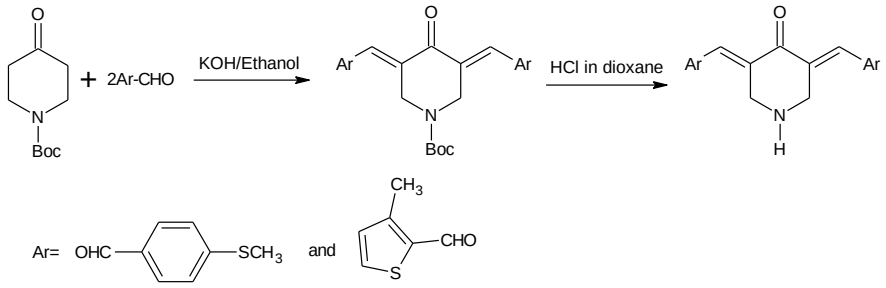
was confirmed by FTIR, ^{1}H NMR, ^{13}C NMR and mass spectral data analysis. Some of the single crystals diffracted by XRD and their structural information was analyzed. The three-dimensional sketch of close contacts in a crystal is acquired from Hirshfeld surface analysis. This chapter demonstrates the synthesis**,** characterization, single crystal XRD and Hirshfeld surface analysis of novel chalcone dibromides. Both chalcones and chalcone dibromides serve as precursors to the synthesis of isoxazoles **[Scheme 3]** and triazolothiadiazines **[Scheme 4]** respectively. It was thought to test their ability to bind anticancer target by molecular docking studies and the compounds which emerge with high binding affinity would be synthesized. The isoxazole and triazolothiadiazine scaffolds from 4-ethoxysubstituted chalcones and chalcone dibromides were designed and subjected for molecular docking simulation. Molecular docking was carried out on the active site of target inhibitor bound cytochrome P450 family oxidoreductase [PDB:3PM0] for breast cancer and pirin inhibiting [PDB: 3ACL] target for skin cancer respectively for both analogues. From the docking analysis performed for isoxazole and triazlothiadiazine analogues, the compounds with halo substitutions emerged with highest docking score compared with other analogues and it was planned to synthesize those analogues with halogen substitution. The compounds are characterized by, FTIR, ^{1}H NMR, ^{13}C NMR, elemental analysis and mass spectroscopic techniques.

CHAPTER IV: NONLINEAR OPTICAL PROPERTIES OF NEW CHALCONE DIBROMIDES

The novel nonlinear optically active chalcone dibromides with diverse substitutions were investigated for third order nonlinear optical properties. This chapter describes the third order nonlinear optical properties with UV-Visible spectroscopy and energy gap calculations. The other parameters such as energy gap, hardness, chemical potential and electronegativity were calculated theoretically. The newly synthesized chalcone dibromides were subjected to measure third harmonic generation (THG) optical parameters by Z-scan technique.

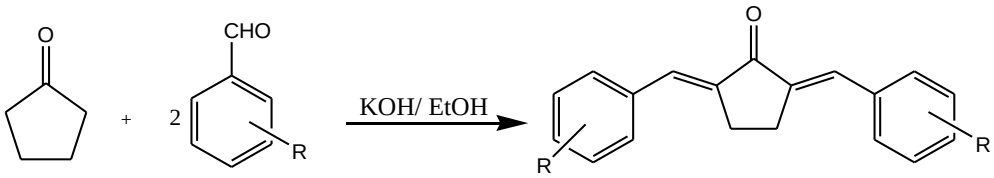
CHAPTER V: OPTICAL STUDIES ON BISCHALCONE DERIVATIVES AND THEIR NANOCOMPOSITES

The describes the synthesis, characterization of piperidone derived bischalcones as wide bandgap semiconductors. In this chapter revisiting of the Donor-π-Acceptor-π-Donor class of 2, 5-dibenzylidenecyclopentan-1-one bischalcone derivatives for third order nonlinear optical parameters and photoluminescence was undertaken. The chloro substituted bischalcone with high quantum efficiency was doped to electrospun nanofiber composite of DNA/PVA. This nanocomposite showed better photoluminescence property with yellow luminescence.



Scheme 5: Synthesis of pipyridone bischalcones

The two novel bischalcone derivatives **[Scheme 5],** were obtained by the reaction of 1-Boc-4-piperidone with 4-methylthiobenzaldehyde and 3-methylthiophene-2-aldehyde using ethanol in basic medium via the *Claisen-Schmidt condensation. The structure of the newly synthesized compounds was determined by FTIR and* ^{1}*H NMR analysis.* Optical and electronic band gap energy were calculated by Tauc's plot and HOMO-LUMO analysis respectively.



R= 4-F, 4-Cl, 4-Br, 3-NO_2

Scheme 6: Synthesis of 2, 5-dibenzylidenecyclopentan-1-ones

This chapter narrates the synthesis **[Scheme 6],** spectral characterization, nonlinear optical (NLO) and optoelectronic investigations of 2,5-dibenzylidenecyclopentan-1-one (bischalcone) analogues. Bischalcones were prepared by base-catalyzed Claisen–Schmidt condensation of cyclopentanone with substituted aldehydes in alkaline medium. Optical transitions and optical emission efficiencies along with band gap of the material were attained by UV–Visible and Photoluminescence (PL) spectroscopy techniques respectively. Optical and electronic band gap energy were calculated by Tauc's plot and HOMO-LUMO analysis. The third-order nonlinear optical measurements of bischalcone analogues carried out by Z-scan technique, which revealed that these compounds possessed strong third-order nonlinear absorption (NLA), negative nonlinear refraction (NLR) and optical limiting behaviour under the illumination at 532nm continuous wave laser beam (200mW). Quantum Mechanics Module of the Materials Science Suite was operated to calculate optoelectronic properties of all compounds. The Flour Tools.com software was used to determine the absolute theoretical quantum yield of the compounds.

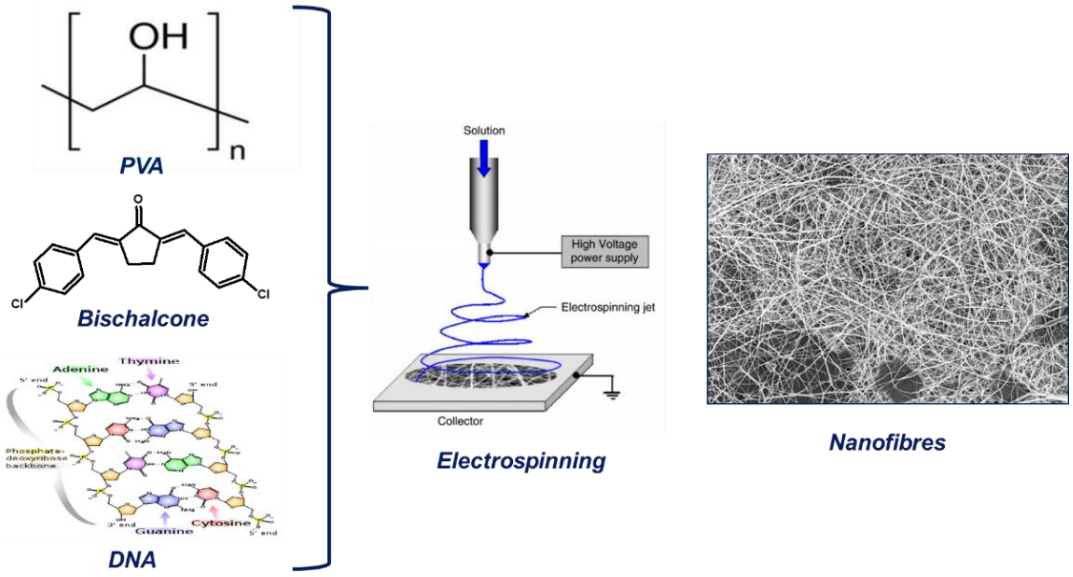


Figure 2: Electrospinning of DNA/PVA with dopant bischalcone

The nanofibers formed were characterized by FT-IR, field emission scanning electron microscopy (FESEM), energy dispersive X-ray (EDX) spectroscopy, UV-Visible spectroscopy and Photoluminescence. The bischalcone doped PVA/DNA nanofiber

showed wide spectrum of emission range 550-650nm. These wide emission band could be attributed to the minor groove binding of bischalcones into DNA helix which was responsible to yellow luminescence. To attain the aspired electrospinnable viscosity a solution comprising polymer blend of PVA (80%) and DNA (20%) was formulated. The concentration of the dopant was retained 2%. The feed compositions of PVA/DNA and bischalcone loaded PVA/DNA**.** The 5ml solutions of PVA/DNA and bischalcone loaded PVA/DNA was fed into a glass syringe and latter it was placed 15cm away from the drum collector. The solution was treated with 15 kV and the speed of the drum collector was maintained at 1200rpm. The flow rate was maintained to 0.5 mL/h

2. OUTCOME OF THE WORK

- Differently substituted chalcones, bischalcones, chalcone dibromides, isoxazoles and triazolothiadiazines were synthesized.
- All the compounds were well characterized by spectroscopic analysis.
- The single crystal X-ray analysis of some of the compounds were carried out wherever diffractable crystals were obtained.
- *In vitro* cytotoxic studies revealed the potency of chalcone analogues towards breast and skin cancer cell lines.
- The third order nonlinear optical properties of Donor-π-Acceptor-π-Donor class of bischalcone derivatives and chalcone dibromides in DMF demonstrated

efficient up conversion with optical nonlinearities and exhibit negative nonlinear refractive index.

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4. LIST OF RESEARCH PAPERS PUBLISHED IN JOURNALS AND PRESENTED IN CONFERENCES

[1] **K.R. Harshitha,** B.K. Sarojini, B. Narayana, S.R. Maidur, P.S. Patil, K. Kumara, **(2019)**, Donor-π-Acceptor-π-Donor class of 2,5-dibenzylidenecyclopentan-1-one analogues as efficient third order nonlinear optical and photoluminescent materials – An experimental investigation, *Optics and Laser Technology.* 117, pp 304–315. DOI: https://doi.org/10.1016/j.optlastec.2019.04.026

[2] **K.R. Harshitha,** B.K. Sarojini, B. Narayana, A.G. Lobo, B.S. Kalal, **(2020)**, Molecular Docking of 4-ethoxychalcones on oxidoreductase/pirin inhibitors and cytotoxic evaluation on breast/skin cancer cell lines, *Letters in Drug Design and Discovery.* 17, pp 1245-1260. DOI: 10.2174/1570180817666200129143803

[3] **K.R. Harshitha,** B.K. Sarojini, B. Narayana, A.G. Lobo, S.M. Kumar, K. Byrappa, **(2018)**, Single crystal X-ray studies and Hirshfeld surface analysis of ethoxy phenyl substituted chalcone derivatives, *Chemical Data Collections.* 17, pp 121-131. DOI: https://doi.org/10.1016/j.cdc.2018.08.002

[4] **K.R. Harshitha,** B.K. Sarojini, **(2019),** Drug-Receptor Interactions of New Isoxazole Scaffold against Breast and Skin Cancer Cell Lines, *Advanced Materials Proceedings.* 4 pp 119-121.

[5] **K.R. Harshitha**, B.K. Sarojini, S.M. Kumar, **(2019),** Engineering a novel optical material chalcone dibromide for optoelectronic applications, *Proceedings of NCASEM-2019 Conference.* pp 348-352.

[6] **K.R. Harshitha**, B.K. Sarojini, **(2020),** Donor-Acceptor-Donor (DAD) Type Pipyridinonyl Bischalcone Derivatives as Promising UVA Filters, AIP Conference Proceedings. 2244, pp 040001(1)- 040001(4). DOI: https://doi.org/10.1063/5.0009078

[7] **K.R. Harshitha,** B.K. Sarojini, B. Narayana, S.M. Kumar, K. Byrappa **(2017)** Spectroscopic, single crystal XRD analysis of novel chalcone derivatives, National Conference on Role of Organic Chemical Intermediates in Cognitive Disorders and Mental Health, NITTE University, Deralakatte, Mangaluru, February 17-18. **Received Best Poster Award-First Place.**

[8] **K.R. Harshitha,** B.K. Sarojini **(2017)** Revisiting bischalcones for photoluminescence activity, National Conference on Reaching the Unreached through Science and Technology: Recent Advances in Physical, Chemical, Mathematical and Biological Sciences for Energy, Health and Environment, Mangalore University, Mangalagangothri, September 8–9.

[9] **K.R. Harshitha,** B.K. Sarojini **(2017)** Green synthesis of α-bromochalcones and 1, 2, 4 –triazolo [3, 4, - b] thiadiazines derived from them for cytotoxic activity, International Conference on Emerging Trends in Chemical Sciences (ICETCS), Manipal Institute of Technology, Manipal, September 14-16.

[10] **K.R. Harshitha,** B.K. Sarojini **(2018)** Drug-receptor interactions of new Isoxazole scaffold against breast and skin cancer cell lines, International Conference on Materials and Spectroscopy (ICMS-2018), Saveetha Engineering College, Chennai, December 11-12. **Received Best Poster Award.**

[11] **K.R. Harshitha,** B.K. Sarojini, B. Narayana, A.G. Lobo **(2019)** Studies on molecular docking and molecular dynamic simulation of synthetic equivalents of flavanoids on breast and skin cancer targets with cytotoxic evaluation, National Conference on Secondary Metabolites and Healthcare, Alva's College, Moodubidire, February 23. **Received Best Oral Award-Second Place.**

[12] **K.R. Harshitha,** B.K. Sarojini **(2019)** Synthesis, spectroscopy, single crystal XRD and Drug-receptor interactions of chalcone dibromide scaffold against breast (3PM0) and skin (3ACL) cancer targets, International Conference on Advanced Functional Materials for Energy, Environment and Health Care (AFMEEHC-2019), University of Mysore, Mysore, March 18-20. **Received Best Oral Award-First Place.**

[13] **K.R. Harshitha,** B.K. Sarojini, S.M. Kumar **(2019)** Engineering a novel optical material chalcone dibromide for optoelectronic applications, National Conference on Advances in Science Engineering and Management-19 (NCASEM-19), Vivekananda College of Engineering & Technology, Puttur, August 23-24.

[14] **K.R. Harshitha,** B.K. Sarojini **(2019)** Donor-Acceptor-Donor (DAD) Type Pipyridinonyl Bischalcone Derivatives as Promising UVA Filters, International Conference on Physics of Materials and Nanotechnology (ICPN 2019), Mangalore University, Mangalagangothri, September 19-21.

[15] **K.R. Harshitha,** B.K. Sarojini, B.S. Holla **(2019)** In silico evaluation of new Triazolo [3,4-b]-thiadiazine derivatives for anti-Alzheimer disease, International Conference on advances in Chemical and Materials Science (ICCM-2019), Mangalore University, Mangalagangothri, October 17-19.

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